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Veterinary Medicines and Inspections

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**COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE
(CVMP)**

**CVMP STRATEGY ON ANTIMICROBIALS 2006-2010
AND
STATUS REPORT ON ACTIVITIES ON ANTIMICROBIALS**

DISCUSSION AT CVMP	December 2005 January and February 2006
ADOPTION BY CVMP	15 March 2006

CVMP STRATEGY ON ANTIMICROBIALS 2006-2010

This *CVMP Strategy on Antimicrobials for 2006-2010* builds on the CVMP work on antimicrobials initiated in late 1990's: The CVMP adopted in 2000 its Risk Management Strategic Plan for controlling antimicrobial resistance through authorisation of veterinary medicines (EMEA/CVMP/818/99-Final). The aim was to develop and implement a comprehensive Risk Management Strategic Plan, which would lead to the development of principles, guidelines and measures to ensure the authorisation of antimicrobial products for veterinary use so that the use of these products is efficient, whilst safeguarding against the development of resistance. In 2003, having reviewed the implementation of the Risk Management Strategic Plan, the CVMP drew attention – among other issues – to the need to collect data on consumption of antimicrobials in Europe (Informal CVMP meeting, Athens, 20 and 21 May 2003: Future strategy on antimicrobial resistance, EMEA/CVMP/558/03-Final). With the actions of the Risk Management Strategic Plan now almost completed (see *CVMP Status report on the activities on antimicrobials*) in the annex to this document, which summarises the current status of work, the CVMP sets out a strategy for its work on antimicrobials for the next 5 years.

The CVMP considers maintaining the efficacy of antimicrobials and minimising the development of resistance one of the most important tasks in the field of veterinary medicine. The measures, which are considered to be necessary to reach these goals, should be balanced so that the availability of necessary antimicrobial veterinary medicinal products is not unnecessarily restricted. This is especially important for the medicinal products, which are used for indications, for which there are no other alternatives available for efficacious treatment.

A. Marketing authorisation of antimicrobial veterinary medicinal products

In the EU, the dossier requirements for veterinary medicinal products are laid down in Directive 2001/82/EC, as amended¹. Development of guidelines for the applicants and assessors is a task of the CVMP. In the field of antimicrobials harmonised interpretation of dossier requirements is particularly vital throughout the EU and should be independent of the marketing authorisation procedures (centralised, decentralised, mutual recognition and national procedures). In order to ensure this, beside the provision of adequate guidance efficient training of assessors is considered important.

The focus of the CVMP work will be in the prudent use instructions, which are considered an efficient way for controlling resistance development through the authorisation of veterinary medicines. Antimicrobials should remain available for the treatment of animal diseases, but at the same time maintaining the efficacy of antimicrobials is vitally important, and the right balance needs to be found. The impact of new requirements and new guidelines should be carefully considered taking into account the interests of all key players, while keeping in mind at the same time that there is an urgent need to actively combat the development of antimicrobial resistance, the appropriate use of antimicrobials should be instructed using recommendations, while applying legal restrictions should only be considered as last option. This approach places high responsibility to the users of antimicrobial veterinary medicinal products especially when medicated premixes or other oral products for the treatment of groups of animals are used.

Following the adoption and implementation of the harmonised VICH guideline GL27 on pre-approval information for registration of new veterinary medicinal products for food producing animals with respect to antimicrobial resistance (CVMP/VICH/644/01), work is going on to prepare further guidance on how to interpret the data requested and when to provide additional information. The guidance will also provide consistency and transparency in the interpretation of pre-approval data.

¹ Directive 2001/82/EC on the Community code relating to veterinary medicinal products, as amended by Directive 2004/28/EC of the European Parliament and of the Council of 31 March 2004 .
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It is recognised that there is a need to develop further guidance for orally administered products. This should also include considerations about the maximum treatment periods and possibilities to further use PK-PD modelling in the establishment of the best dose and dosing regimen.

The CVMP will actively follow the available information on antimicrobial resistance in the EU including the data from surveillance programmes and EU zoonosis reports. The availability of information on the overall use of antimicrobials from the Member States is very important when considering suitable instructions for prudent use for different types of products. Besides, there is a need to obtain data on the level of the use of antimicrobials per species, especially for fluoroquinolones and extended-spectrum cephalosporins.

The need to revise or update guidance or to recommend any measures, where appropriate or necessary, will be actively considered, and in this process the CVMP will use expertise in its scientific advisory group on antimicrobials (SAGAM) and different working parties. This strategy will be transferred to activities of the SAGAM and/or working parties and outlined in their working programmes.

The CVMP will enhance the communication with other parties² especially EFSA, ECDC, FVE and veterinary medicines industry in order to more efficiently exchange information on resistance issues and usage of antimicrobials.

The CVMP will also be actively involved in the scientific debate on antimicrobials and will have an open dialogue with other parties about the efforts, which are necessary to maintain the efficacy of antimicrobials.

Following the publication of its *Reflection Paper on the use of Fluoroquinolones in Food-Producing Animals in the European Union: Development of Resistance and Impact on Human and Animal Health* (EMEA/CVMP/SAGAM/184651/05) for consultation, which was prepared with the support of the SAGAM, the CVMP will finalise its review on the need to exercise certain control on those classes of compounds of greater importance to human medicine for fluoroquinolones and will embark on a similar activity in respect to other groups of antimicrobials, in particular 3rd and 4th generation cephalosporins.

B. International activities in the field of antimicrobials

The CVMP will work actively to strengthen its expert role in the field of antimicrobials which are used and required for the treatment of animal diseases. The CVMP has identified that there is a need to provide more input into the international debate regarding the development of antimicrobial resistance. Active networking of experts is seen as playing an important role to achieve this aim.

There is a need to have a better understanding on the developments in the field of antimicrobials on a global scale, thus the CVMP will take further initiative and explore possibilities to liaise with the regulatory authorities outside the EU, in particular those of the United States and Japan, on antimicrobial issues.

C. Future developments

The CVMP acknowledges that within the field of antimicrobials changes of the situation can occur quickly in particular due to emergence of resistance, changes in use patterns of antimicrobials and the need to have new possibilities for treatment of infectious diseases in animals. The CVMP will have a continuous focus on this important area, and will review and update this strategy, when appropriate, and in any case a new strategy will be published in the year 2010 at the latest.

² In the field of antimicrobials, the CVMP co-operates with other regulators (Commission, Member States, EFSA, ECDC), veterinary medicinal industry, veterinarians, representatives of animal owners, consumer groups as well as medical professionals, FAO and WHO.

CVMP STATUS REPORT ON ACTIVITIES ON ANTIMICROBIALS

SUMMARY

In order to facilitate the development of the new CVMP strategy on antimicrobials for 2006-2010, this CVMP status report on activities on antimicrobials (2005) has been prepared for reviewing the activities carried out after the adoption of the previous *risk management strategic action plan for controlling antimicrobial resistance through authorisation of veterinary medicines* (EMEA/CVMP/818/99) in 2000.

The CVMP has considered the problem of antimicrobial resistance in several instances since late 1990's and many of the actions were carried out in accordance to the CVMP strategic action plan including the development of several guidelines or the revision of existing guidelines. Having efficacious antimicrobials available for the treatment of infectious animal diseases and minimising the development of resistance have been the main goals of the CVMP. The current regulatory practices of the European Union are mirrored against the principles set out in the *Guidelines for the responsible and prudent use of antimicrobial agents in veterinary medicine* of the OIE. Although good progress has been made since 2000 there is still room for further improvement.

REVIEW OF PROGRESS AFTER THE RISK MANAGEMENT ACTION PLAN OF THE CVMP OF 2000

The CVMP adopted the *risk management strategic plan for controlling antimicrobial resistance through the authorisation of veterinary medicine* (EMEA/CVMP/818/99³) in 2000. Having the Plan in place for more than five years, the CVMP agreed in April 2005 to revise and update its strategy on antimicrobials with the main focus on controlling the development of resistance. In order to facilitate the development of the new CVMP strategy on antimicrobials for 2006-2010, this CVMP status report on activities on antimicrobials has been prepared for reviewing the activities carried out since the adoption of the risk management strategic action plan in 2000.

The CVMP strategic action plan summarised the following eight areas of activities.

Strategic action plan	CVMP actions taken
1. Review the risk assessment process to identify the areas where direct action is possible and highlight the significant gaps in data currently available.	Addition of dossier requirements to assess effects on zoonotic organisms: Guideline on pre-authorisation studies to assess the potential for resistance resulting from the use of antimicrobial veterinary medicinal products (EMEA/CVMP/244/01-FINAL-corr ⁴). This guideline was later replaced by the VICH (International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products) harmonised Guideline GL27. Guidance on Pre-Approval Information for Registration of New Veterinary Medicinal Products for Food Producing Animals

³ <http://www.emea.eu.int/pdfs/vet/regaffair/081899en.pdf>

⁴ <http://www.emea.eu.int/pdfs/vet/swp/024401en.pdf>
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	with Respect to Antimicrobial Resistance (CVMP/VICH/644/01-Final ⁵).
2. Communicate the conclusion of this review to other interested parties, especially in those areas where data deficiencies are outside the remit of the CVMP.	CVMP press releases, consultation procedure for guidelines, Infodays, publication of Future Strategy on Antimicrobial Resistance in 2003 after the informal CVMP meeting in Athens ⁶ .
3. Put in place guidelines detailing the data requirements for the assessment process, to ensure the risk of antimicrobial resistance developing can be adequately defined.	Besides the guidelines under “action 1” ^{4,5} the guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances (EMEA/CVMP/627/01) and the guideline on the SPC for antimicrobial products (EMEA/CVMP/612/01)
4. Ensure a consistent approach, in terms of product information supplied to the end user and public, to ensure effective prudent use of antimicrobials)	The guideline on the SPC for antimicrobial products (EMEA/CVMP/612/01) was developed; assessor training on efficacy to gain consistent interpretation of guidelines
5. Identify infectious diseases where immunological products or husbandry changes would have a significant impact by reducing the volume of antimicrobials used.	Outside of the remit of the CVMP.
6. Comment on these areas where research and data collection is intended, to ensure it informs the assessments of risk and improves the management of risk through regulatory controls.	Conclusions and recommendation of Antibiotic resistance in the European Union associated with therapeutic use of veterinary medicines – Report and qualitative risk assessment by the Committee for Veterinary Medical Products (EMEA/CVMP/342/99. Guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances (EMEA/CVMP/627/01 ⁷), the guideline on the SPC for antimicrobial products (EMEA/CVMP/612/01 ⁸) and GL27 Guidance on Pre-Approval Information for Registration of New Veterinary Medicinal Products for Food Producing Animals with Respect to Antimicrobial Resistance (CVMP/VICH/644/01-Final ⁵). CVMP input into WHO, OIE, VICH and Codex meetings.
7. Communicate and co-ordinate CVMP activity with other interested parties to ensure a consistent, effective approach to the problem of antimicrobial resistance.	The CVMP has organised various meetings with interested parties including a Focus Group meeting (14 November 2003) and a meeting with CHMP members in Madrid (3 December 2002)
8. Advise the Commission of significant ‘political issues’ and their potential impact on the ‘risk management plan’ of the CVMP.	The Commission has consistently being requesting input and technical advice from the CVMP on issues relating to antimicrobials and veterinary medicinal products and reporting on their activities (see informal meeting in Greece, 20-21 May 2003 ⁶)

It is concluded that the CVMP with the support from its Working Parties has been able to fulfil the activities detailed the Strategic Plan except the number 5, which is now considered to be outside of the remit of the CVMP.

⁵ <http://vich.eudra.org/hm/guidelines.htm> and <http://www.emea.eu.int/pdfs/vet/vich/064401en.pdf>

⁶ <http://www.emea.eu.int/pdfs/vet/regaffair/055803en.pdf>

⁷ <http://www.emea.eu.int/pdfs/vet/ewp/062701en.pdf>

⁸ <http://www.emea.eu.int/pdfs/vet/ewp/061201en.pdf>

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OTHER DEVELOPMENTS ON ANTIMICROBIAL ISSUES

The CVMP has considered the problem of antimicrobial resistance in several instances since late 1990s, detailed information on different activities of the CVMP can be found in the EMEA web page <http://www.emea.eu.int/hmts/vet/swp/srantimicrobial.htm>. The document “*Antibiotic resistance in the European Union associated with therapeutic use of veterinary medicines – Report and qualitative risk assessment by the Committee for Veterinary Medical Products (EMEA/CVMP/342/99⁹)*” was finalised in July 1999. This document concluded – among other things – that:

- the increase in prevalence of resistance will inevitably lead to problems with the selection of antibiotics available and their efficacy,
- animals undoubtedly represent a source of antibiotic-resistant micro-organisms for humans (and vice versa) and prudent use of antibiotics is therefore needed in veterinary as well as in human medicine.

Besides the activities of the CVMP since late 1990s, the EU Council delivered a Council Resolution of 8 June 1999 on antibiotic resistance “*A strategy against the microbial threat*” (1999/C 195/01)¹⁰. This resolution considered that antibiotic resistance and its various causes need a multidisciplinary and cross-sectorial approach. An overall strategy should be based on risk assessment using known scientific principles, keeping in mind a precautionary approach, and comprise coordinated control and preventive action and research on several areas. Among these actions promotion of prudent use of antibiotics is highlighted.

The European Commission also considered the problem of antimicrobial resistance and has delivered the *Communication from the European Commission on a community strategy against antimicrobial resistance*¹¹ (20 June 2001). This communication states - among other proposals - that containment of antimicrobial resistance should include consolidation and standardisation of phrases and formats used in the Summary of Product Characteristics to define clearly and consistently throughout the European Union posology/treatment regimes, target organisms and diseases in accordance with prudent use principles.

Internationally antimicrobial resistance is an ongoing subject for discussion and these are also taken into account when preparing the future CVMP strategy. At FAO/OIE/WHO meetings in Geneva (2003)¹² and Oslo (2004)¹³, the existing knowledge on the risks of non-human use and the potential risk management’s options was discussed. It was concluded that antimicrobial agents are essential drugs for human and animal health and welfare and that antimicrobial resistance is a global public health concern that is impacted by both human and non-human antimicrobial usage. The OIE expert group (January 2005, Paris, France) and WHO expert Drafting Group (February 2005, Canberra, Australia) drafted criteria for critically important antimicrobials for veterinary and human¹⁴ use, respectively. The preparation of critically important antibacterial agents for human medicine for risk management strategies of non-human use could also have some implications for the veterinary use. While it is difficult to anticipate exactly what might be deemed appropriate in terms of regulatory actions (such as inserting specific statements regarding use into some SPCs of licensed and future antibacterial agents), there could be some pressure on the CVMP to at least consider this possibility following the sequential deliberations currently planned. The CVMP will continue to follow these

⁹ <http://www.emea.eu.int/pdfs/vet/regaffair/034299ENC.pdf>

¹⁰ http://europa.eu.int/eur-lex/pri/en/oj/dat/1999/c_195/c_19519990713en00010003.pdf

¹¹ http://europa.eu.int/comm/health/ph/others/antimicrob_resist/am_02_en.pdf

¹² <http://www.who.int/foodsafety/publications/micro/nov2003/en/>

¹³ <http://www.who.int/foodsafety/publications/micro/mar04/en/>

¹⁴ The WHO expert group had agreed a following definition for critically important antibacterial agents for man:

a) the agent should be the sole treatment or among a few alternatives for the treatment of serious human disease AND

b) the agent should be used to treat disease caused by organisms that may be transmitted *via* non-human sources or diseases caused by organisms that may acquire resistance genes from non-human sources

international developments. At the same time, the CVMP acknowledges that the antimicrobial products are crucial in the combat of infectious animal diseases.

The CVMP notes that the use of antimicrobials in human medicine contributes to resistance in human pathogens. This is, however, outside of the scope of tasks of the CVMP and should be handled by human medical experts. Therefore, the CVMP considers that it is important that the veterinary experts should concentrate on measures aiming to minimise the resistance development due to use of antimicrobials in veterinary medicine. This is also the most effective way to ensure that there are efficacious antimicrobials for the treatment and prevention of infectious animal diseases.

The structure of this document follows the principles and order of the tasks for regulatory authorities, which has been detailed in the *Guidelines for the responsible and prudent use of antimicrobial agents in veterinary medicine* of the OIE¹⁵. The CVMP has also taken a note of the adoption of the code of practice to minimize and contain antimicrobial resistance (CAC/RCP 61-2005¹⁶). This CVMP document covers the antimicrobials used for all animal species.

The CVMP agrees with the OIE goals of the prudent use of antimicrobials i.e.

OIE text: Prudent use includes a set of practical measures and recommendations intended to prevent and/or reduce the selection of antimicrobial-resistant bacteria in animals to:

1. maintain the efficacy of antimicrobial agents and to ensure the rational use of antimicrobials in animals with the purpose of optimising both their efficacy and safety in animals;
2. comply with the ethical obligation and economic need to keep animals in good health;
3. prevent, or reduce, as far as possible, the transfer of micro-organisms (with their resistance determinants) within animal population;
4. maintain the efficacy of antimicrobial agents used in food-producing animals;
5. prevent or reduce the transfer of resistant micro-organisms or resistance determinants from animals to humans;
6. maintain the efficacy of antimicrobial agents used in human medicine and prolong the usefulness of the antimicrobials;
7. prevent the contamination of animal-derived food with antimicrobial residues that exceed the established maximum residue limit (MRL);
8. protect consumer health by ensuring the safety of food of animal origin with respect to residues of antimicrobial drugs, and the ability to transfer antimicrobial drug resistant micro-organisms to humans.

RESPONSIBILITIES OF THE REGULATORY AUTHORITIES

1. Marketing authorisation

In the EU, a marketing authorisation can be applied for through different procedures (centralised procedure, mutual recognition procedure, decentralised procedure and national procedure), which means that there is a need for harmonised decisions on indications, warnings and prudent use guidance despite the procedure, which is used to authorise the antimicrobial product.

It is noted that on the basis of experience gained from the application of existing guidelines there is a need for revision and further development of guidelines for dossier requirements and assessment criteria as well as guidance how to provide information for the user in the Summary of Product Characteristics (SPC) and product literature.

¹⁵ Terrestrial Animal Health Code, Edition 2005: chapter 3.9.3
http://www.oie.int/eng/normes/mcode/en_chapitre_3.9.3.htm

¹⁶ Code of practice to minimize and contain antimicrobial resistance CAC/RCP 61-2005
<http://www.ipfsaph.org/id/codex10213?language=en>

2. Submission of data for the granting of the marketing authorisation

In the EU, the legal basis is set out in the Community legislation and the dossier requirements are detailed in the Directive 2001/82/EC of the European Parliament and of the Council as amended¹⁷. Besides, there are several guidelines on quality, safety and efficacy, which the applicant should take into account when preparing the dossier.

This is in line with the OIE recommendations (article 3.9.3.3. point 2):

OIE text: The pharmaceutical industry has to submit the data requested for the granting of the marketing authorisation. The marketing authorisation is granted only if the criteria of safety, quality and efficacy are met. An assessment of the potential risk and benefits to both animals and humans resulting from the use of antimicrobial agents in food-producing animals should be carried out. The evaluation should focus on each individual antimicrobial product and the findings not be generalised to the class of antimicrobials to which the particular active principle belongs. Guidance on usage should be provided for all dose ranges or different durations of treatment that are proposed.

3. Marketing approval

The Commission - based on the recommendation in this respect of the CVMP - grants marketing authorisations through the centralised procedure. This CVMP opinion is given on the basis of the scientific data and proposal are made to include necessary risk management measures in order to limit the risk of development of antimicrobial resistance (instruction on administration, dosage and dosing interval).

In the national procedure, mutual recognition procedure and decentralised procedure, regulatory authorities of the Member States grant the marketing authorisations. Introduction of necessary instructions, warnings and guidance is also their responsibility. After 30 October 2005 obligatory arbitration takes place if the Member States cannot reach consensus in the Mutual Recognition or Decentralised procedure, thus the CVMP will be involved in the arbitration procedures more often than before.

The CVMP does not see a need to expedite the marketing authorisation procedures for antimicrobial products. Thorough safety assessment including that of antimicrobial resistance is needed for all antimicrobial products. Conditional authorisation could be considered if the disease had serious consequences (animal health, economical) and is caused by resistant organism, against which there is no antimicrobial treatment available any more. However, in case of substances intended for use in food-producing animal the establishment of MRL is needed.

The CVMP together with other authorities, the Commission and industry as well as with professional organisations has been actively finding ways to improve the availability of veterinary medicinal products for minor users and minor species (MUMS). The availability of antimicrobial products is part of these activities. Draft guidelines addressing dossier requirements for the demonstration of safety and efficacy of products for MUMS have been in consultation until 31 October 2005 and are currently under revision by the CVMP and its Working Parties.

OIE text: Regulatory authorities should attempt to expedite the market approval process of a new antimicrobial in order to address a specific need for the treatment of disease.

¹⁷ Official Journal L 311 , 28/11/2001 P. 0001 - 0066
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4. Registration procedures

In the EU, procedures for assessing the marketing authorisation applications are defined. With continuous assessor training consistent assessment is ensured. Training is also important when implementing new guidelines.

OIE text: Countries lacking the necessary resources to implement an efficient registration procedure for veterinary medicinal products (VMPs), and whose supply principally depends on imports from foreign countries, should undertake the following measures:

- a. check the efficacy of administrative controls on the import of these VMPs;
- b. check the validity of the registration procedures of the exporting and manufacturing country as appropriate;
- c. develop the necessary technical co-operation with experienced authorities to check the quality of imported VMPs as well as the validity of the recommended conditions of use.

Regulatory authorities of importing countries should request the pharmaceutical industry to provide quality certificates prepared by the competent authority of the exporting and manufacturing country as appropriate. All countries should make every effort to actively combat the manufacture, advertisement, trade, distribution and use of unlicensed and counterfeit bulk active pharmaceutical ingredients and products.

The EU supports the need for efficient marketing authorisation procedures throughout the world.

5. Quality control of antimicrobial agents

Sound quality is essential for the safety and efficacy of a veterinary medicinal product. Adequate quality of the veterinary medicinal product ensures batch-to-batch consistency and that the product fulfils the established product specifications to the end of the authorised shelf life. All veterinary medicinal products are manufactured in compliance with the provisions of Good Manufacturing Practices (Volume 4 of the Rules Governing Medicinal Products in the European Union).

OIE text: Quality controls should be performed:

- a. in compliance with the provisions of good manufacturing practices;
- b. to ensure that analysis specifications of antimicrobial agents used as active ingredients comply with the provisions of approved monographs;
- c. to ensure that the quality and concentration (stability) of antimicrobial agents in the marketed dosage form(s) are maintained until the expiry date, established under the recommended storage conditions;
- d. to ensure the stability of antimicrobials when mixed with feed or drinking water;
- e. to ensure that all antimicrobials are manufactured to the appropriate quality and purity in order to guarantee their safety and efficacy.

6. Control of therapeutic efficacy

Date generated from preclinical studies including pharmacodynamic, pharmacokinetic and target animal safety studies are necessary for the establishment of grounds on appropriate dosage regimen to be used in the dose finding and dose confirmation studies. The proof of the efficacy of an antimicrobial product is based upon a demonstration of efficacy in clinical trials.

Several guidelines for products containing antimicrobial substances have been revised after the adoption of strategic management plan and among these guidelines is also *the guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances* (EMA/CVMP/627/01¹⁸), which was adopted in December 2002. When compared to the old guideline this revision provided more guidance for MIC testing, data to be provided on the resistance in target pathogens as well as on planning and reporting of clinical trials. PK-PD modelling was introduced for the first time in the CVMP's antimicrobial guidelines.

¹⁸ <http://www.emea.eu.int/pdfs/vet/ewp/062701en.pdf>
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OIE text:

a. Preclinical trials

i. Preclinical trials should:

- establish the range of activity of antimicrobial agents on both pathogens and non-pathogens (commensals);
- assess the ability of the antimicrobial agent to select for resistance *in vitro* and *in vivo*, taking into consideration pre-existing resistant strains;
- establish an appropriate dosage regimen necessary to ensure the therapeutic efficacy of the antimicrobial agent and limit antimicrobial resistance (Pharmacokinetic and pharmacodynamic data and models can assist in this appraisal.).

ii. The activity of antimicrobial agents towards the targeted micro-organism should be established by pharmacodynamics. The following criteria should be taken into account:

- spectrum of activity and mode of action;
- minimum inhibitory and bactericidal concentrations;
- time- or concentration-dependent activity or co-dependency;
- activity at the site of infection.

iii. The dosage regimens allowing maintenance of effective antimicrobial levels should be established by pharmacokinetics. The following criteria should be taken into account:

- bio-availability according to the route of administration;
- concentration of the antimicrobial at the site of infection and its distribution in the treated animal;
- metabolism that may lead to the inactivation of antimicrobials;
- excretion routes;
- use of combinations of antimicrobial agents should be scientifically supported.

b. Clinical trials

Clinical trials should be performed to confirm the validity of the claimed therapeutic indications and dosage regimens established during the preclinical phase. The following criteria should be taken into account:

- i. diversity of the clinical cases encountered when performing multi-centre trials;
- ii. compliance of protocols with good clinical practice, such as Veterinary International Cooperation on Harmonisation (VICH) guidelines;
- iii. eligibility of studied clinical cases, based on appropriate criteria of clinical and bacteriological diagnoses;
- iv. parameters for qualitatively and quantitatively assessing the efficacy of the treatment.

EU regulations for veterinary medicinal product take into account the above suggestions.

7. Assessment of the potential of antimicrobials to select for resistance

Antimicrobial substances have different potential to select for the development of resistant strains either in target animal pathogens, commensals or in zoonotic bacteria. Resistance development in target animal pathogens is part of efficacy dossier, while resistance development in zoonotic bacteria may cause human safety concerns. The CVMP guideline on providing information on the potential impact of the use of a veterinary medicinal product on antimicrobial resistance in bacteria of animal origin with relevance to human health¹⁹ was adopted in 2002. This was later replaced by the VICH GL 27²⁰, which became into effect in the beginning of 2005. The CVMP has agreed to develop technical guidance on interpretation criteria in order to harmonise the European approach on the assessment of

¹⁹ Guidelines on pre-authorisation studies to assess the potential for resistance resulting from the use of antimicrobial veterinary medicinal products (<http://www.emea.eu.int/pdfs/vet/swp/024401en.pdf>)

²⁰ VICH Harmonised Guideline GL27. Guidance on Pre-Approval Information for Registration of New Veterinary Medicinal Products for Food Producing Animals with Respect to Antimicrobial Resistance. International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products. <http://vich.eudra.org/htm/guidelines.htm> and <http://www.emea.eu.int/pdfs/vet/vich/064401en.pdf>

the data required in accordance with the VICH GL 27²¹. This will provide complementary guidance to the VICH GL 27, as this guideline is focussed at the characterisation of the potential of a drug to select for resistance of public health concern but the guidance for the assessment of the data provided is not included.

Besides the considerations on dossier requirements as described above the CVMP has agreed to explore the need for action on the risk assessment or management aspects in case of certain groups of substances, which are considered to be important in treating critical diseases in humans and when the increase in resistance is related to the use of antimicrobials in treatment of animal diseases. The antimicrobial classes identified include fluoroquinolones and 3rd and 4th generation cephalosporins). The first phase of this evaluation of information deals with fluoroquinolones, the document "Reflection paper on the use of fluoroquinolones in food-producing animals in the European Union: Development of resistance and impact on human and animal health" (EMEA/CVMP/SAGAM/184651/2005-Consultation²²)" has been released in January 2006 for a period of 3 months of public consultation

OIE text: Other studies may be requested in support of the assessment of the potential of antimicrobials to select for resistance. The party applying for market authorisation should, where possible, supply data derived in target animal species under the intended conditions of use.

For this the following may be considered:

- a. the concentration of active compound in the gut of the animal (where the majority of potential food-borne pathogens reside) at the defined dosage level;
- b. the route and level of human exposure to food-borne or other resistant organisms;
- c. the degree of cross-resistance within the class of antimicrobials and between classes of antimicrobials;
- d. the pre-existing level of resistance in the pathogens of human health concern (baseline determination) in both animals and humans.

The OIE recommendations are now included in the VICH GL27 and the CVMP is in a process to provide technical guidance how the requirements of the VICH guideline should be interpreted in the EU.

8. Establishment of acceptable daily intake, maximum residue limits (MRLs) and withdrawal periods for antimicrobial compounds

Foodstuffs obtained from animals treated with veterinary medicinal products must not contain residues of the medicine or its metabolites, which might constitute a health hazard for the consumer, thus the safety of residues is assessed and if necessary, MRLs are established. The legal basis is set in the Council Regulation 2377/90 of 26 June 1990, as amended, and detailed guidance of this process is provided in the Volume 8 of the Rules Governing Medicinal Products in the European Union²³ and the CVMP-VICH guideline GL36 General Approach to establish a microbiological ADI (CVMP/VICH/467/03²⁴). CVMP guidelines²⁵ on the statistical methods for setting withdrawal periods for tissues and for milk are in place to ensure consumer safety.

²¹ Concept paper on Further Guidance on Interpretation of the data from VICH GL27 (CVMP/CVMP/1034/04). Guidance on pre-approval information for registration of new veterinary medicinal products for food producing animals with respect to Antimicrobial resistance (CVMP/VICH/644/01)

²² <http://www.emea.eu.int/pdfs/vet/srwp/18465105en.pdf>

²³ <http://pharmacos.eudra.org/F2/eudralex/vol-8/home.htm>

²⁴ <http://www.emea.eu.int/pdfs/vet/vich/046703en.pdf>

²⁵ Note for Guidance: Approach towards Harmonisation of Withdrawal Periods for Meat EMEA/CVMP/036/95 (<http://www.emea.eu.int/pdfs/vet/swp/003695en.pdf>)

Note for Guidance for the Determination of Withdrawal Periods for Milk EMEA/CVMP/473/98 (<http://www.emea.eu.int/pdfs/vet/swp/047398en.pdf>)

OIE text:

- a. When setting the acceptable daily intake (ADI) and MRL for an antimicrobial substance, the safety evaluation should also include the potential biological effects on the intestinal flora of humans.
- b. The establishment of an ADI for each antimicrobial agent, and an MRL for each animal-derived food, should be undertaken.
- c. For each VMP containing antimicrobial agents, withdrawal periods should be established in order to produce food in compliance with the MRL, taking into account:
 - i. the MRL established for the antimicrobial agent under consideration;
 - ii. the composition of the product and the pharmaceutical form;
 - iii. the target animal species;
 - iv. the dosage regimen and the duration of treatment;
 - v. the route of administration.
- d. The applicant should provide methods for regulatory testing of residues in food.

This is covered by the above-mentioned EU regulations.

9. Protection of the environment

As for any other veterinary medicinal product, the assessment of environmental safety needs to be carried out when the dossier for marketing authorisation is applied. The Phase I guidance detailed in VICH GL6²⁶ describes criteria for determining whether or not an environmental impact assessment should be undertaken. If the exposure limits set are exceeded in the Phase I the Phase II assessment is needed to obtain data on environmental fate, metabolism and toxicity of the active substance using the test methods described in the phase II guideline (VICH GL38²⁷). On the basis of these studies the applicant should propose appropriate risk management measures to mitigate potential adverse environmental effects.

The CVMP is developing guidance on the interpretation of data requirement for environmental safety studies in order to guarantee harmonised assessment of veterinary medicinal products in the EU.

OIE text: An assessment of the impact of the proposed antimicrobial use on the environment should be conducted. Efforts should be made to ensure that the environmental impact of antimicrobial use is restricted to a minimum.

This is covered by VICH guidelines and the CVMP is in a process to provide technical guidance how the requirements of the VICH guideline should be interpreted in the EU.

10. Establishment of a summary of product characteristics (SPC) for each veterinary antimicrobial product (VAP)

The SPC contains the information necessary for the appropriate use of veterinary medicinal products and constitutes the official reference for their labelling and package insert. In principle, the risk assessment and risk management should be separated from each other, but the CVMP opinion on marketing authorisation application or on variation should contain the SPC and other product information, which should include all the necessary warnings and instructions for prudent use. The same principle applies to the other authorisation procedures in place in the EU because besides the SPC also the texts for package insert and labelling are agreed during the mutual recognition procedure and decentralised procedure after 30 October 2005.

²⁶ VICH GL6. Environmental Impact Assessment (EIAs) for veterinary medicinal products (VMPs) – Phase 1. (<http://vich.eudra.org/htm/guidelines.htm>)

²⁷ VICH GL38. Draft Environmental Impact Assessment (EIAs) for veterinary medicinal products (VMPs) – Phase II (<http://vich.eudra.org/htm/guidelines.htm>)

The general guidance for the preparation of the SPC is in the Notice to Applicants (under revision in October 2005). In addition, there has been a CVMP guideline on SPC for antimicrobials products in place since June 2003. The revision of this guideline has been agreed in the CVMP and should be published for public consultation during 2006. In the SPCs for the products containing antimicrobials, which are also considered to be important in treating critical diseases in humans should contain appropriate warnings (fluoroquinolones, 3rd and 4th generation cephalosporins).

OIE text: The summary of product characteristics contains the information necessary for the appropriate use of VAPs and constitutes the official reference for their labelling and package insert. This summary should contain the following items:

- a. active ingredient and class;
- b. pharmacological properties;
- c. any potential adverse effects;
- d. target animal species and age or production category;
- e. therapeutic indications;
- f. target micro-organisms;
- g. dosage and administration route;
- h. withdrawal periods;
- i. incompatibilities;
- j. shelf-life;
- k. operator safety;
- l. particular precautions before use;
- m. particular precautions for the proper disposal of un-used or expired products.
- n. information on conditions of use relevant to the potential for selection of resistance

This is covered by the EU legislation and guidelines detailed above.

11. Post-marketing antimicrobial surveillance

Specific surveillance

The CVMP has set as a post-marketing authorisation commitment a requirement for resistance surveillance for some centrally authorised products. The debate is on-going if this provides any useful information about the resistance development and in March 2005 CVMP the SAGAM was asked to advice the CVMP²⁸. This advice should cover products, which are authorised via national and mutual recognition procedure, besides those authorised via centralised procedure. Besides the resistance data also data on consumption should be collected. For each product this consumption data are available in PSURs but it is important to compile overall consumption figures for active substances used. This is outside of the tasks of the CVMP but the importance of this has been highlighted several times by the CVMP.

In the Strategic Action Plan in 1999²⁹ a proposal was made to develop a guideline for post marketing surveillance using MIC breakpoints or other methods to evaluate resistance in the field. Actions to be taken if breakpoints/limits are exceeded should also be identified. Meanwhile the OIE has adopted a guideline on resistance surveillance as a part of Terrestrial Code³⁰ thus it there is no need for the CVMP to develop such a guideline. However, there is a need to consider which actions are necessary if resistance shows increasing trends.

²⁸ March 2005 CVMP: Problem statement on the approach to be followed on antimicrobial resistance surveillance as post-marketing authorisation commitment (EXT/118542/2005)

²⁹ Point 4(i)c in the *risk management strategic plan for controlling antimicrobial resistance through the authorisation of veterinary medicine* (EMEA/CVMP/818/99)

³⁰ http://www.oie.int/eng/normes/mcode/en_sommaire.htm
EMEA/CVMP/353297/2005

General epidemiological surveillance

Several European countries have set up their national surveillance programs for drug usage and resistance³¹. Besides, in order to harmonize monitoring and reporting on *Salmonella* and *Campylobacter*, the EU has in 2003 obliged the Member States to monitor antimicrobial resistance in these zoonotic organisms³².

This EU-funded project, ARBAO-II, aims to harmonize the susceptibility testing of bacteria from food-producing animals in a network of national veterinary reference laboratories in Europe. The project involves 19 laboratories in 18 European countries.

The CVMP strongly supports such activities although are outside its scope of action.

OIE text: The information collected through existing pharmacovigilance programmes, including lack of efficacy, should form part of the comprehensive strategy to minimise antimicrobial resistance. In addition to this, the following should be considered:

a. General epidemiological surveillance

The surveillance of animal micro-organisms resistant to *antimicrobial agents* is essential. The relevant authorities should implement a programme according to the *Terrestrial Code*.

b. Specific surveillance

Specific surveillance to assess the impact of the use of a specific antimicrobial may be implemented after the granting of the marketing authorisation. The surveillance programme should evaluate not only resistance development in target animal pathogens, but also in food-borne pathogens and/or commensals. Such surveillance will also contribute to general epidemiological surveillance of antimicrobial resistance.

12. Supply and administration of the antimicrobial agents used in veterinary medicine

In the Strategic Action Plan adopted in 2000³³ a proposal was made that all antimicrobial products should be subject to veterinary prescription in the EU. According to the article 67a of the directive 28/2004 all veterinary medicinal products for food-producing animals should be prescription-only-medicines after the 1st of January 2007 thus the harmonised approach will be guaranteed for the products for food-producing animals. This has also been the case for the products authorised via centralised procedure there still are products authorised nationally in the EU member states, for which a prescription is not required. For these products, the prescription status is the responsibility of the national authorities.

OIE text: The relevant authorities should ensure that all the antimicrobial agents used in animals are:

- a. prescribed by a veterinarian or other authorised person;
- b. supplied only through licensed/authorised distribution systems;
- c. administered to animals by a veterinarian or under the supervision of a veterinarian or by other authorised persons;
- d. the relevant authorities should develop effective procedures for the safe collection and destruction of unused or expired VAPs.

³¹ DANMAP in Denmark, NORM/NORM-VET in Norway, SVARM/SWEDRES in Sweden FINRES-Vet in Finland, MARAN in the Netherlands, ITAVARM in Italy and REMOST in Austria. Surveillance programs exist also in France, Germany, Spain and the UK.

³² Directive 2003/99/EC of the European Parliament and the Council on the monitoring of zoonoses and zoonotic agents, amending Council Decision 90/424/EEC and repealing Council Directive 92/117/EEC. Official Journal L 325, 12.12.2003. <http://europa.eu.int/eur-lex/en/search/index.html>.

³³ Point 4(i)g in the *risk management strategic plan for controlling antimicrobial resistance through the authorisation of veterinary medicine* (EMEA/CVMP/818/99)

13. Control of advertising

Rules about advertising have not been harmonised in the EU but after 30 October 2005 prescription-only-medicines may not be advised to the general public according to the article 85(2) of the Directive 28/2004. This should harmonise the advertising practises in the EU although it is noted that there are no harmonised rules what should be included in the advertising material. The CVMP supports the development of harmonised advertising practices.

It is the task of the regulatory authorities in the Member States to control that the advertising is done in accordance with the national legislation in place. For nationally authorised products, the prescription status is responsibility of the national authorities thus this issue is related to that. The discussion is required with the HMA-V.

OIE text: All advertising of antimicrobials should be controlled by a code of advertising standards, and the relevant authorities must ensure that the advertising of antimicrobial products:

- a. complies with the marketing authorisation granted, in particular regarding the content of the summary of product characteristics;
- b. is restricted to authorised professionals, according to national legislation in each country.

14. Training of antimicrobial users

In the Strategic Action Plan adopted in 2000³⁴ it was proposed to develop a policy to ensure clear, targeted claims for new and existing antimicrobials to encourage effective usage. Veterinarians should have full understanding of the importance of information provided in the SPC and product literature. The revision of the SPC guideline was aimed to help to achieve this goal.

OIE text: The training of users of antimicrobials should involve all the relevant organisations, such as regulatory authorities, pharmaceutical industry, veterinary schools, research institutes, veterinary professional organisations and other approved users such as food-animal owners. This training should focus on:

- a. information on disease prevention and management strategies;
- b. the ability of antimicrobials to select for resistance in food-producing animals;
- c. the need to observe responsible use recommendations for the use of antimicrobial agents in animal husbandry in agreement with the provisions of the marketing authorisations.

15. Research

In the Strategic Action Plan in 1999³⁵ a proposal was made to identify infectious diseases that have a major impact on antimicrobial usage and would benefit from the development of alternative control methods (e.g. immunological products). The primary focus could be zoonotic diseases. It is considered that this is outside of tasks of the CVMP. The EFSA has worked on documents on *Salmonella* control methods and the Commission is changing the legislation on *Salmonella* controls, thus there are on-going EU activities on this field. All efforts to improve diagnosis of infectious animal diseases are also important because this could have marketed effect in the use of antimicrobials. Finding effective alternative measures for the use of antimicrobials are also needed. Also the research on mechanism of resistance, spread of infections and resistance determinants etc. is important to better understand the ways to control infectious diseases.

³⁴ Point 4(i)e in the *risk management strategic plan for controlling antimicrobial resistance through the authorisation of veterinary medicine* (EMEA/CVMP/818/99)

³⁵ Point 4(i)i in the *risk management strategic plan for controlling antimicrobial resistance through the authorisation of veterinary medicine* (EMEA/CVMP/818/99)

According to the Strategic Action Plan adopted in 2000³⁶ where new immunological products or new husbandry standards are introduced or where new risk management procedures are adapted, monitoring to measure their effect should be considered. Such effects may include reductions in a use/consumption of antimicrobials and the development of resistance. Although the CVMP strongly support those actions, this is outside of tasks of the CVMP.

OIE text: The relevant authorities should encourage public- and industry-funded research.

³⁶ Point 4(i)j in the *risk management strategic plan for controlling antimicrobial resistance through the authorisation of veterinary medicine* (EMEA/CVMP/818/99)
EMEA/CVMP/353297/2005